EDITORIAL
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NIPPLE SPARING: STANDARD OF CARE?

Poupadora de mamilos: padrão de cuidado?

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INTRODUCTION

Over the past several decades, advances in the treatment of breast cancer have led to less radial types of surgery for both the breast and the axilla. First, the concept of breast-conserving therapy was introduced, followed by the adoption of sentinel lymph node biopsy to largely replace axillary lymph node dissection. For patients who require mastectomy, techniques have evolved from radial and modified radical mastectomy (MRM) to procedures which facilitate reconstruction and improve cosmesis: skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM). While both approaches remove the glandular breast tissue, SSM preserves the majority of the skin flap, and NSM additionally preserves the nipple areolar complex (NAC). Preservation of the NAC has been associated with improved body image, satisfaction with nipple appearance and sensitivity, and higher psychosocial and sexual well-being in patients who undergo NSM compared with SSM[1,2]. Recent studies have confirmed the oncologic safety of NSM and its successful application for risk reduction in patients at high risk for breast cancer[3-5]. Complication rates in recent years are comparable to those for other types of post-mastectomy reconstruction, likely a result of improving surgeon experience and wider application of NSM technique[3,5]. Given the continuously increasing rates of bilateral mastectomy and high demand for breast reconstruction[6], we must ask whether NSM should now be considered standard of care.

ONCOLOGIC SAFETY

Initial concerns regarding the safety of NSM from an oncologic perspective stemmed from the perceived risk of recurrence at the NAC due to preserved ductal tissue, as well as risk of local recurrence owing to incomplete removal of glandular tissue secondary to limitations of the technique. Among single-institution studies of patients undergoing NSM, local recurrence rates range from 2–11.7%, with recurrence in the NAC of 1.3–3.7%[7]. A pooled analysis of 73 studies including 12,358 NSM procedures reported an overall locoregional recurrence rate of 2.38% at mean follow-up of 38 months (range 7.4–156 months)[4]. At longer average follow-up of 78 months for 788 NSM patients, Sakurai et al.[8] demonstrated a local recurrence rate of 8.2% and a nipple relapse rate of 3.7%, but no significant difference was found in overall or disease-free survival between patients who underwent NSM compared to conventional mastectomy at 21 years. Similarly, the study with the longest mean follow-up to date of 101 months (range 32–126 months) reported similar rates of recurrence for patients undergoing SSM (10.4%), NSM (11.7%), and MRM (11.5%), with no significant differences in rates of distant metastasis or breast cancer-specific mortality[9]. The current literature therefore supports the oncologic safety of NSM, and ongoing studies with longer follow-up will continue to inform recommendations for its use in patients with breast cancer.

RISK REDUCTION

Due to its aesthetic appeal and potential for bilateral application, NSM is a particularly attractive option for risk reduction in patients at high risk of breast cancer secondary to BRCA 1/2 mutations or strong family history. In the small number of studies which have retrospectively examined outcomes after bilateral NSM for risk reduction, subsequent breast cancer was diagnosed in 0–1.2% of patients[7]. Yao et al.[10] assessed incidental cancers, complications, and locoregional recurrences in 201 BRCA 1/2 mutation carriers who underwent either prophylactic or therapeutic NSM. At mean follow-up of 32.6 months (range 1–76 months), there were four total cancer events, only one of which was in a risk-reduction patient, and none involved the NAC. In a review of 728 NSMs performed at Memorial Sloan Kettering Cancer Center between 2000 and 2013, 459 (63%) were risk reducing, and 177 (24%) were in patients with a BRCA 1/2 mutation or a genetic variant of uncertain significance[5]. At median follow-up of 49 months, there were no cases of local recurrence, and only one case of regional recurrence which was in a patient who underwent therapeutic NSM. The vast majority of patients in both studies underwent immediate reconstruction with low complication rates and favorable short-term outcomes. While longer-term results are needed to

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confirm these findings, current evidence supports the use of NSM for risk reduction in BRCA 1/2 carriers and other patients at high risk for breast cancer.

PATIENT OUTCOMES

Factors which motivate NSM include improvement in aesthetic outcomes and patient satisfaction associated with preservation of the NAC. Studies demonstrate that patients who undergo NSM have better body image, overall satisfaction, and psychosocial well-being when compared with patients who undergo SSM with or without nipple reconstruction[1,2,9]. Results from survey-based analyses describe overall satisfaction with modern NSM in 68–77% of patients, with nipple appearance rated as good or excellent in 66–88%, but nipple sensation rated good or excellent in only 10–40%[7]. Interestingly, there was a significant decrease in surgeons' rating of aesthetic outcome after both SSM and NSM with increasing time interval from surgery, though patient ratings did not change significantly over the same period[9]. However, as others have pointed out, satisfaction scores vary considerably based on methodology and survey instrument, and may be adversely affected by post-operative complications.

Complications of NSM are similar to those of SSM when combined with immediate reconstruction and include infection, hematoma, flap necrosis, implant loss, and capsular contracture; necrosis and loss of the NAC are, however, unique to NSM. The recent meta-analysis by Headon et al.[4] reported an overall complication rate of 22.3% with an incidence of partial or total nipple necrosis of 5.9%. This is higher than the 1.8% rate of NAC loss found in the study by Yao et al., the latter of which is more reflective of recent data showing a low rate of nipple loss (0.9–1.9%) in contemporary series[7,10]. While NSM has been associated with a higher rate of flap necrosis, most series report resolution without need for operative debridement, and rates of expander or implant loss of less than 4%[5,11]. Importantly, complication rates have decreased over time to a mean of 11.5% in studies published after 2013, likely reflecting greater operative experience with NSM technique and careful application to appropriately selected patients[4].

PATIENT SELECTION AND OTHER CONSIDERATIONS

For the first time in 2016, the U.S. National Comprehensive Cancer Network (NCCN) suggested that performance of NSM could be considered in selected patients with breast cancer with the following characteristics: early-stage, biologically-favorable invasive cancer or ductal carcinoma in situ (DCIS) at least 2 cm from the nipple (i.e., Nottingham grade 1 or 2, node-negative, HER2 negative, no lymphovascular invasion), with no evidence of malignancy at nipple margin assessment[12]. Absolute contraindications to NSM include pathologic nipple discharge, skin or nipple involvement such as Paget's disease or inflammatory carcinoma, and imaging findings suggesting malignant involvement of the nipple and subareolar tissues.

Studies assessing post-operative complications have identified additional factors which are variably adopted as relative contraindications to NSM. Smoking, prior radiation to the chest wall, and previous breast surgery affect tissue viability and may impair wound healing. Very large and/or ptotic breasts may increase the risk of flap and nipple necrosis and create a reconstructive challenge due to excess skin in the preserved envelope[13]. Patients who are obese or have multiple medical co-morbidities are not ideal candidates for NSM due to the increased risk of complications with complex surgery, reconstruction, and the associated longer operative time. However, in recent years, NSM has been used more widely in groups previously excluded from consideration, for example, in selected patients following neoadjuvant chemotherapy, and in those with prior breast incisions or macromastia[3,7].

One critical caveat to the ongoing discussion regarding oncologic, surgical, and patient-centered outcomes after NSM is the relative lack of long-term data. While the current evidence supports its use in well-selected patients, more robust follow-up is needed to determine its safety and efficacy in the wider population of women who may desire NSM.

CONCLUSIONS

Compared with SSM and MRM, NSM provides the advantage of preserving the NAC and maintaining its unique native color, size, and projection, characteristics which are difficult to reproduce with reconstructed nipples[13]. Loss of the NAC is considered by some to be as or even more psychologically significant than loss of the breast mound, which is readily replaced by either implant-based or autologous reconstruction. Given the greater overall satisfaction and psychosocial well-being reported in patients undergoing NSM compared with SSM, NSM should undoubtedly be considered when a patient requires or chooses mastectomy.

When evaluating whether a new procedure or treatment should be adopted as standard of care, it must be assessed for safety and efficacy. In addition, it must be not only non-inferior to the current standards, but also possess an element that is superior in some way—by decreasing morbidity or mortality, or by improving quality of care. NSM meets the latter criteria in providing superior patient-centered outcomes, favorable aesthetic results, and a gain in quality of life compared with the other types of mastectomy[14]. Both meta-analyses and single-institution studies have confirmed the oncologic safety of NSM in selected patients, and the NCCN supports its use in patients with early-stage, biologically favorable, peripheral breast cancer with negative nipple margins at histopathological assessment[4,5,11]. NSM is also efficacious for risk reduction in patients with BRCA

1/2 mutations and those at high risk of breast cancer, with low rates of recurrence and complications[7,10]. The major complication unique to NSM is necrosis of the NAC, the rate of which has decreased in recent years. Though undesirable, NAC loss essentially converts an NSM to an SSM, which does not compromise the therapeutic or prophylactic outcome from an oncologic standpoint. NSM is safe and efficacious, non-inferior to existing mastectomy techniques, and provides an added benefit to patients in psychosocial domains, thereby meeting the stipulations for a new standard of care.

However, it must be noted that NSM is not indicated for all patients, just as other "standards" such as sentinel lymph node biopsy are applied only in the appropriate clinical setting. NSM requires negative nipple margin assessment and must not be pursued in patients with carcinoma known or suspected to invade the NAC or subareolar tissue by clinical exam, presence of nipple discharge, or imaging findings. NSM should be carefully considered in patients with multiple co-morbidities, current smokers, and those who have had prior breast surgery or radiation. Close coordination with reconstructive surgery must be sought in such cases to minimize complications by planning appropriate incisions and perhaps performing staged procedures.

Given the rising incidence of both therapeutic and prophylactic bilateral mastectomies and the likelihood of identifying greater numbers of patients at high risk of breast cancer due to genetic testing, the demand for NSM is likely to increase. We must ensure that breast and reconstructive surgeons fully understand the indications and contraindications to this technique, and appropriately counsel patients regarding both oncologic and aesthetic outcomes. This should include discussing the limitations of short-term follow-up in the majority of studies, as well as potential operative complications, and the risks and benefits of NSM compared with SSM. However, with careful patient selection, shared decision making, and coordination of care, NSM can be confidently adopted in a subset of patients as standard of care for the treatment of breast cancer and for the reduction of breast cancer risk.

REFERENCES

1. Didier F, Radice D, Gandini S, Bedolis R, Rotmensz N, Maldifassi A, et al. Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality? Breast Cancer Res Treat. 2009;118(3):623-33. https://doi.org/10.1007/s10549-008-0238-4
2. Wei CH, Scott AM, Price AN, Miller HC, Klassen AF, Jhanwar SM, et al. Psychosocial and sexual well-being following nipple-sparing mastectomy and reconstruction. Breast J. 2016;22(1):10-7. https://doi.org/10.1111/tbj.12542
3. Galimberti V, Vicini E, Corso G, Morigi C, Fontana S, Sacchini V, et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast. 2017; 34(Suppl 1):S82-S84. https://doi.org/10.1016/j.breast.2017.06.034
4. Headon HL, Kasem A, Mokbel K. The oncological safety of nipple-sparing mastectomy: A systematic review of the literature with a pooled analysis of 12,358 procedures. Arch Plast Surg. 2016;43(4):328-38. https://doi.org/10.5999/aps.2016.43.4.328
5. Manning AT, Sacchini VS. Conservative mastectomies for breast cancer and risk-reducing surgery: the Memorial Sloan Kettering Cancer Center experience. Gland Surg. 2016;5(1):55-62. https://doi.org/10.3978/j.issn.2227-684X.2015.10.02
6. Jagsi R, Jiang J, Momoh AO, Alderman A, Giordano SH, Buchholz TA, et al. Trends and variation in use of breast reconstruction in patients with breast cancer undergoing mastectomy in the United States. J Clin Oncol. 2014;32(9):919-26. https://doi.org/10.1200/JCO.2013.52.2284
7. Hieken TJ, Boolbol SK, Dietz JR. Nipple-sparing mastectomy: indications, contraindications, risks, benefits, and techniques. Ann Surg Oncol. 2016;23(10):3138-44. https://doi.org/10.1245/s10434-016-5370-5
8. Sakurai T, Zhang N, Suzuma T, Umemura T, Yoshimura G, Sakurai T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. Med Oncol. 2013;30(1):481. https://doi.org/10.1007/s12032-013-0481-3
9. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. Ann Surg. 2009;249(3):461-8. https://doi.org/10.1097/SLA.0b013e31819a044f
10. Yao K, Liederbach E, Tang R, Lei L, Czechura T, Sisco M, et al. Nipple-sparing mastectomy in BRCA1/2 mutation carriers: an interim analysis and review of the literature. Ann Surg Oncol. 2015;22(2):370-6. https://doi.org/10.1245/s10434-014-3883-3
11. Piper M, Peled AW, Foster RD, Moore DH, Esserman LJ. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. Ann Plast Surg. 2013;70(4):435-7. https://doi.org/10.1097/SAP.0b013e31827e5333
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology by Site: Breast Cancer [Internet]. [cited on July 26, 2017]. Available at: www.nccn.org
13. Spear SL, Hannan CM, Willey SC, Cocilovo C. Nipple-sparing mastectomy. Plast Reconstr Surg. 2009;123(6):1665-73. https://doi.org/10.1097/PRS.0b013e3181a64d94
14. Mota BS, Riera R, Ricci MD, Barrett J, de Castria TB, Atallah AN, et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. Cochrane Database Syst Rev. 2016;11:Cd008932. https://doi.org/10.1002/14651858.CD008932.pub3